a sincere effort to expedite prosecution, applicants have amended the claims to refer to the Type I TNF receptor as having at least the amino acids 3-163 of SEQ ID NO:1.

The USPTO has emphasized that the art is "unpredictable." The USPTO has not stated what aspect(s) of the art is unpredictable, or whether it believes everything that takes place in the art is unpredictable, such is not clear from the Action. Certainly, some unpredictability must exist in this art, or in *every* art for that matter, otherwise there would be no need to perform any experiments whatsoever. Without regard to applicants' statements of record, the USPTO wants applicants to provide absolute predictability about which deletions or substitutions will work and which will not work. Without such predictions presented in a specification, the USPTO asserts that one of ordinary skill in the art would not be not enabled to make and use a claimed invention. Applicants disagree that such a requirement is the law and believe their specification satisfies the correct interpretation of §112(1).

As applicants have stated previously, making of the claimed proteins having deletions or substitutions between amino acids 3-163 would not require undue experimentation. Such techniques are certainly routine in the art - an assertion not refuted by the USPTO with objective evidence. It is well settled that the performance of routine tasks does not equate with "undue experimentation" under the law. Reference is made to the 20-year old seminal case *In re Angstadt*, 190 USPQ 214 (CCPA 1976). Because *Angstadt* is directly on point with the instant situation, applicants describe that fact situation. The appellant claimed a catalytic process, and the examiner, with the Board affirming, rejected the claims under §112(1) and stated:

> the specification states that not all of the complexes will produce hydroperoxides and neither discloses which of the complexes will not work nor gives any information as to how the operative catalysts might be determined, without undue experimentation. We believe the specification leaves too much conjecture, speculation and experimentation... [190 USPQ 216]

To begin its analysis, the Court reviewed §112(1) and stated that pursuant to the enablement requirement, a specification needed a disclosure of "how to make" and "how to use" the claimed invention. Looking at the facts of the case, the Court then acknowledged the unpredictability of catalytic processes and stated that the scope of enablement varies inversely with the degree of unpredictability. The Court stated at page 218:

> the question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. *** such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. [emphsis in original]
>
> [h]aving decided that appellants are not required to disclose every species encompassed by their claims even in an unpredictable art ... each case must be determined on its own facts.

> [a]ppellants have, in effect, provided those skilled in the art with a large but finite list of transition metal salts from which to choose in preparing a complex catalyst. [one of skill in the art] would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. [emphasis added]

Here, as in *Angstadt*, applicants have provided those of ordinary skill in the art a finite list of "bioequivalent analogs" that are possible. See the applicants' specification at pages 6 et seq. These analogs can be made using routine procedures and, like *Angstadt*, do not require unusual reaction conditions or special equipment to make. As further support for applicants' position, applicants provide a Rule 1.132 Declaration of Dr. Virginia Price. Dr. Price declares that such mutagenesis methods are old and well established in the art. She also states that the description in the specification would have allowed one of ordinary skill in the art to routinely make and test such analogs without the use of undue experimentation. The Price Declaration alone is sufficient to rebut the USPTO's rejection of non-enablement. Indeed, the declaration sets forth objective factual evidence, see *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996) that places the burden on the USPTO to demonstrate how applicants' specification fails to enable the ordinary skilled artisan to make and use the claimed invention.

The Court in Angstadt finally states at page 219:

> [if the disclosure must provide] guidance which will enable one skilled in the art to determine, with *reasonable certainty before performing the reaction*, whether the claimed product will be obtained ... then *all* "experimentation" is "undue", since the term "experimentation" implies that the success of the particular activity is *uncertain*. Such a proposition is contrary to the basic policy of the Patent Act. [emphasis in original]

The USPTO has argued that based on applicants' specification, a person of ordinary skill in the art would not know which mutations would work. That statement may be true in some circumstances, however, the law states that applicants need not provide absolute assurance of success. Indeed, *Angstadt* holds:

> in this art, **the performance of trial runs using different catalysts is "reasonable", even if the end result is uncertain,** and we see no reason on this record why appellants should not be able to claim as their invention the broad range of processes which they have discovered. [emphasis added]

Should the USPTO choose to rebut the value of *Angstadt*, it must provide evidence as, the Court held:

> showing that the disclosure entails *undue* experimentation is part of the PTO's initial burden ... this court has never held that evidence of the necessity for *any* experimentation, however slight, is sufficient to require the applicant to prove

> that the type and amount of experimentation needed is *not* undue. [emphasis added.]

Lastly, and importantly, *Angstadt,* at page 219, held that if the end result is a failed process, then nobody will use it and the claims do not cover it:

> [w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them. [emphasis added]

Like the catalysts in *Angstadt*, analogs of the TNF receptors that do or do not work will be readily discovered. See the Price Declaration. The USPTO has nowhere in the record refuted this fact. In addition, nobody will use them and reading the claim language, the claims will not cover them. Like the Board's decision which was reversed by the Court in *Angstadt*, the USPTO here is requiring the applicants to provide absolute predictability of the invention. The Courts held this as improper 20 years ago and it is still the law today.

Therefore, dealing with the specific issues raised in the Action, at page 3, the USPTO asserts that conservative substitutions require undue experimentation. No scientific support is provided. Indeed, Dr. Price declares that the USPTO's assertions are incorrect. Furthermore, the USPTO alleges that "applicants' in vivo data is not conclusively correlated with a reduction in disease." However, on the same page at the bottom, the USPTO states: "the declaration filed ... is considered sufficient to overcome the objection to the claims concerning the statistical significance of the data." These contradictory statements must be rectified. Does the USPTO believe the utility of the methods, or does it not? The Declaration by Dr. Moreland, of record, conclusively proves the utility in vivo of the claimed method. The USPTO has acknowledged this. In view of the evidence of record, withdrawal of the rejection is respectfully requested.

II. THE SPECIFICATION ENABLES ONE OF ORDINARY SKILL IN THE ART TO MAKE AND USE THE CLAIMED METHOD FOR INHIBITING TNF ACTIVITY IN A MAMMAL

The USPTO has raised a new grounds of rejection. The claims now recite a method for inhibiting TNF, and during the May 9 interview, this was indicated as being more acceptable to the USPTO. Applicants believe this new rejection is moot in view of the interview conducted on May 9 with the Examiner and in view of the amendments above. Applicants do not acquiesce to the rejection in any way and believe new claim 10 obviates the new rejection as being moot.

The USPTO has already agreed that the disclosure enables one of ordinary skill in the art to make and use the claimed invention for treating arthritis. This is specifically claimed in new claim 11. Applicants submit that the method for treating other TNF-mediated diseases involves no additional enablement under §112. Indeed, applicants believe the new rejection exists because the USPTO requires applicants to provide absolute predictability of in vivo utility in all clinical indications. The only "support" provided by the USPTO for the rejection is

a editorial article by Steiner et al. It is respectfully submitted that the Steiner et al. editorial is not relevant in any respect to the instant situation. Indeed, Steiner et al. make an antithetical statement that:

> [t]he spectacular successes of biotech have mostly been souped-up hormones or enzymes--EPO or Neupogen, Activase, Pulmozyme, or Ceredase-- use in disease precesses where mechanisms of action are straightforward. However, companies that seek to tinker with complex cascades of cytokines, neurotransmitters, parahormones, *whatever*, **have got a cruising for a bruising.** [emphasis added]

Applicants first disagree that this editorial should be used as a reference or in any way to establish the alleged absolute unpredictability of the art. It was published in 1994, two years after the filing date of the instant application. Secondly, there is nothing on the record to establish that the authors are of ordinary skill in the art. The article is simply an editorial, a commentary. Applicants specifically request the USPTO provide a §1.107(b) showing of how Steiner et al. rise to the level of one of ordinary skill in the art. Finally, what exactly is meant by the phrase "cruising for a bruising" and how does that relate to patent law and more specifically to enablement? The USPTO has not provided this information. The USPTO must demonstrate the legal meaning of this phrase. Applicants respectfully submit that the authors are not of ordinary skill in the art since the quoted statement is internally contradictory and Steiner et al.'s statements do not seem objectively based. The contradiction is apparent in that Steiner et al. state that EPO and Neupogen are involved in a "straightforward mechanism of action." However, Steiner et al. fail to recognize that erythropoietin (EPO) and Neupogen **ARE** cytokines - the kind that Steiner et al. assert involves "complex cascades." This is the exact type of therapy the authors urge that companies have got a "cruising for a bruising." Furthermore, Leukine® or sargramostim, is a human GM-CSF (also a cytokine) approved by the FDA for treating patients undergoing, *inter alia*, a bone marrow transplant. Clearly, the opinions of Steiner et al. are not based on fact. How then can the USPTO believe the authors are of ordinary skill in the art when their statements are not based on fact? If the USPTO maintains this rejection, applicants request the Examiner provide a Rule 107(b) declaration that objectively demonstrates how and why the authors would be considered of ordinary skill, and why their statements are not antithetical. Withdrawal of the Steiner article is requested as is withdrawal of the rejection.

III. THE CLAIMS ARE NOT RENDERED OBVIOUS IN VIEW OF BRENNAN, HARRIS AND SMITH SINCE HARRIS AND SMITH ARE NOT PRIOR ART AND BRENNAN DO NOT DISCLOSE TNFRS

The claims stand rejected under 35 U.S.C. §103 as allegedly obvious over Brennan, Harris and Smith. This rejection is maintained from previous office actions despite applicants urging that Harris and Smith are not available as prior art.

Smith et al. was published on May 25, 1990, and Harris et al. was published on May 3, 1990. Reviewing the priority documents resolves this issue. For example, in serial no. 523,635 filed May 10, 1990, now U.S. Patent No. 5,395,760, it is disclosed:

1) column 2, lines 62-66: "The present invention also provides compositions for use in therapy, diagnosis, assay of TNF, or in raising antibodies to TNF-R, comprising effective quantities of soluble native or recombinant receptor proteins prepared according to the foregoing processes."

2) column 2, line 67 to column 3, line 6: "Because of the ability of TNF to specifically bind TNF receptors (TNF-R), purified TNF-R compositions will be useful in diagnostic assays for TNF, ... diagnosis and therapy. In addition, purified TNF receptor compositions may be used directly in therapy to bind or scavenge TNF, thereby providing a means for regulating the immune activities of this molecule."

3) column 3, lines 41-43: "... and which are biologically active, as defined below, in that they are capable of binding TNF molecules ..."

4) column 3, lines 63-64: "... retain the ability to bind TNF..."

5) column 4, lines 20-21: "... in that they bind to TNF..."

6) column 5, lines 23-24: "... capable of binding detectable quantities of TNF..."

7) column 10, lines 53-68: "A recombinant chimeric antibody molecule may also be produced having TNFR sequences substituted for the variable domains of either or both of the immunoglobulin molecule heavy and light chains and having unmodified constant region domains. For example, chimeric TNFR/IgG$_1$ may be produced from two chimeric genes -- a TNFR/human k light chain chimera (TNFR/C$_k$) and a TNFR/human g$_1$ heavy chain chimera (TNFR/C$_{g-1}$). Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNFR may have enhanced binding affinity for TNF ligand. Additional details relating to the construction of such chimeric antibody molecules are disclosed in WO 89/09622 and EP 315062.

8) column 16, line 57 - column 17, line 25: Therapeutic Administration of Recombinant Soluble TNFR
"The present invention provides methods of using therapeutic compositions comprising an effective amount of soluble TNF-R proteins and a suitable diluent and carrier, and methods of suppressing TNF-dependent inflammatory responses in humans comprising administering an effective amount of soluble TNF-R protein.
"For therapeutic use, purified soluble TNFR protein is administered to a patient, preferably a human, for treatment in a manner appropriate to the indication. Thus, for example, soluble TNFR protein compositions can be administered, for example by bolus injection, continuous infusion, sustained release from implants, or other suitable techniques. Typically, a soluble TNFR therapeutic agent will be administered in the form of a composition comprising purified protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNFR with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins,

(continuation of disclosure in 523,635 filed May 10, 1990, now U.S. Patent No. 5,395,760):

amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth."

9) entire Example 1

Clearly, applicants have sufficient support in U.S. Patent 5,395,760 (USSN 523,635) to obtain the benefit of its May 10, 1990 filing date. Such entitlement is sufficient to remove Smith et al. as prior art.

In application serial no. 421,417, filed October 13, 1989, for example, it is disclosed:

1) page 2, lines 34-35: "... and which are biologically active, as defined below, in that they are capable of binding TNF molecules ..."

2) page 4, lines 3-4: "... capable of binding detectable quantities of TNF..."

3) page 13, lines 12-21: "TNFR-compositions are prepared for administration by mixing TNF-R having the desired degree of purity with physiologically acceptable carriers. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNF-R with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates, including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients.
"TNF-R compositions may be used to attenuate TNF-mediated immune responses. To achieve this result, a therapeutically effective quantity of a TNF-R composition is administered to a mammal, preferably a human, in association with a pharmaceutical carrier or diluent."

4) entire Example 1

Clearly, applicants have sufficient support in USSN 421,417 to obtain the benefit of its October 13, 1989 filing date. Such entitlement is sufficient to remove both Harris et al. and Smith et al. as prior art.

Whether applicants are claiming a method of treating TNF-mediated inflammatory diseases or a method of inhibiting TNF in a mammal as currently claimed, the priority documents establish that Smith et al. and Harris et al. are not available as prior art. Applicants therefore are entitled to the benefit of their earlier filing dates, especially at least as early as the October 13, 1989 date which antedates both Smith et al. and Harris et al.

Having removed all but Brennan et al. from the rejection, applicants will establish that the obviousness rejection cannot stand based on the disclosure of Brennan et al. As established in the record, Brennan et al. disclose only an anti-TNF antibody. No disclosure or suggestion

of a TNF receptor is made. Indeed, on July 29, 1989, the date Brennan et al. published, the TNF receptor was not known to have been cloned or completely purified. Therefore, it would be impossible for Brennan et al. to disclose or suggest a molecule that was not known to be in existence in a purified, working form.

Withdrawal of the rejection over Brennan et al., Harris et al. and Smith et al. is respectfully requested in view of applicants entitlement to the claimed priority dates and the inapplicability of Brennan et al. to the invention.

IV. THE CLAIMS ARE NOT RENDERED OBVIOUS IN VIEW OF BRENNAN, HARRIS, CAPON, HOOGENBOOM IN VIEW OF SMITH

The claims stand rejected under 35 U.S.C. §103 as allegedly obvious over Brennan, Harris, Capon, Hoogenboom in view of Smith. Applicants respectfully traverse. In view of applicants' entitlement to their claimed priority dates, Harris et al., and Smith et al. are not available as prior art. Hoogenboom also is not available as prior art since it was not published until 1991, two years after applicants' priority date. The remaining documents that can only be relied upon are Capon and Brennan et al. It has been established that Brennan et al. disclose ONLY anti-TNF antibodies. The USPTO concedes this and states at page 6 of the Action: "The Brennan reference essentially copies the instant invention with a different molecule" [emphasis added].

Capon discloses LHR:Fc fusions. Capon also generically state that "ligand-binding partners" may be fused to Fc regions. However, Capon's definition of a "ligand-binding partner" at column 7, line 35 et seq. does not define a ligand-binding partner by what it is, rather it defines it by what it is not. Capon goes on to provide a list of what is not considered to be a ligand-binding partner. No specific, affirmative recitation of what is included in that generic definition is provided by Capon. Indeed, the only specifics provided by Capon are for LHR:Fc fusions. LHR is not a TNF receptor. Thus, the generic description of what is not a ligand-binding partner Capon cannot be said to disclose or suggest TNF receptor as claimed. Indeed, like Brennan et al., as of effective date of Capon et al., the TNF receptor was not even known to have been cloned or completely purified. There had not been any public disclosures about TNF receptor at that time. Therefore, like Brennan et al., it would be impossible for Capon et al. to disclose or suggest a molecule that was not known to be in existence in a purified, working form. Withdrawal of the rejection is respectfully requested.

V. INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR 1.56, 1.97 and 1.99, applicants bring to the USPTO's attention the following document: United States Patent No. 5,344,915 ('915) to LeMaire et al. covering a monomeric TNF receptor protein. The '915 patent is based on a PCT application, and its effective date as a reference under 35 USC 102(e) is September 26, 1991. Even though

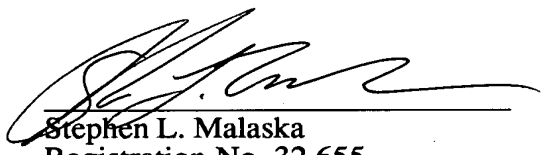
applicants do not believe the '915 patent discloses or suggests the claimed invention, the '915 patent, like the documents cited above, is not available as prior art against applicants' invention.

Because citation of this document is after the issuance of the first Office Action, applicants authorize the Commissioner to charge applicants' deposit account no. 09-0089 in the amount of $210.00, as set forth in 37 CFR 1.17(p).

VI. SUMMARY

In summary, applicants believe claims 3 and 10-13 are in condition for allowance and respectfully request the issuance of a favorable action upon reconsideration.

Respectfully submitted,



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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date indicated below.

Date: May 23, 1996 Signed: Nancy M. Kertson